

The relationship between serum vitamin D levels and dry eye syndrome in postmenopausal women

Vitamin D and dry eye

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Abstract

Aim: In this study, we aimed to investigate the association between serum vitamin D levels and dry eye signs and symptoms in postmenopausal women. **Material and Method:** Postmenopausal women with severe vitamin D deficiency (Group 1, n=30), moderate deficiency (Group 2, n=27) and those with optimal serum vitamin D levels (Group 3, n=30) were recruited for this cross-sectional study. Dry eye complaints were evaluated by the Ocular Surface Disease Index (OSDI) questionnaire and dry eye signs were evaluated by the Schirmer's test I, the Tear break up time (TBUT) test, and ocular surface fluorescein staining. **Results:** The mean vitamin D level of the Group 1 was 7.82 ± 1.80 ng/ml, that of the Group 2 was 15.88 ± 1.70 ng/ml and Group 3 was 33.47 ± 7.00 ng/ml. The percentages of patients diagnosed as dry eye were 53.33% for Group 1, 44.44% for Group 2, and 33.33% for Group 3 ($p=0.29$). There was no statistically significant difference between Group 1 (37.55 ± 19.20), Group 2 (43.58 ± 16.79), and Group 3 (40.87 ± 21.32) in respect to the mean OSDI scores. In addition, there was no any statistically significant difference between the three groups in terms of the mean TBUT (Group 1: 7.73 ± 3.25 secs, Group 2: 6.78 ± 2.99 secs and Group 3: 6.70 ± 3.37 secs) and Schirmer's test I scores in (Group 1: 9.30 ± 4.86 mm, Group 2: 8.07 ± 4.09 mm and Group 3: 9.40 ± 5.49 mm) ($p=0.33$ vs $p=0.72$). Eight patients (26.7%) in Group 1, 5 patients (18.5%) in Group 2, and 3 patients (10%) in Group 3 have positive corneal fluorescein staining ($p=0.25$). **Discussion:** Serum vitamin D levels have no association with dry eye complaints evaluated by OSDI questionnaire and tear film deficiency and functional integrity detected by the tests in postmenopausal women.

Keywords

Dry Eye Syndrome; Vitamin D; 25-hydroxyvitamin D; Menopause

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Introduction

Vitamin D is a prohormone in steroid structure and has two major forms D2 (ergocalciferol) and D3 (cholecalciferol). D3 is synthesized in human skin by ultraviolet-B radiation (UVB 290-315nm) and consumed in animal-based food, whereas D2 is derived from plant sources and not human-made. Both forms are biologically inactive and activated by enzymatic hydroxylation in liver 25(OH) D and kidney 1, 25(OH)₂ D. The synthesis of vitamin D is regulated by the parathyroid hormone in response to fluctuations in serum calcium levels. As a fat-soluble vitamin, it breaks down quickly leading to the stores to deplete and hence deficiency. Worldwide an estimated one billion people have inadequate levels of serum vitamin D in all ethnicities and age groups [1].

The action of vitamin D is mediated by the vitamin D receptor (VDR), a subfamily of nuclear receptors which is found virtually in all cell types [2]. This explains the multiple actions of vitamin D in different tissues. Vitamin D has a substantial role in the regulation of calcium and phosphate metabolism and maintenance of healthy bones. Vitamin D has been reported to relieve inflammatory reactions and regulate cell cycles, increase defence capacity of macrophages, inhibit proinflammatory responses of antigen presenting cells and reduce cell cytokines mainly IL-1, IL-6, IL-12, and TNF α and hence has a key role in immune responses of both adaptive and innate immunity [2,3]. Dry eye syndrome (DES) is a multifactorial disorder of the tear film and ocular surface which causes ocular discomfort, pain, redness, irritation, eye fatigue, itching and vision-related complaints [4]. Studies have shown that inflammation is the core mechanism in the pathogenesis of DES and characterized by increased osmolarity of the tear film and inflammation of the ocular surface [5,6]. Activation of inflammatory pathways by proinflammatory cytokines of IL-1 and TNF α in conjunctival, limbal, and corneal epithelial cells plays a critical role in ocular surface inflammation in DES [7]. Supporting this, increased levels of inflammatory cytokines in the tear film, corneal and conjunctival epithelial cells and infiltration of inflammatory CD4⁺ T cells into the conjunctival epithelia have been demonstrated [8]. The generally recognized risk factors for DES include elder age, reproductive factors, contact lens use, refractive surgeries, systemic autoimmune diseases, environmental and occupational factors, drugs (antihistaminics, β -blockers, and estrogens) and recently nutritional factors especially essential fatty acid and vitamin D deficiency [9,10].

We hypothesized that vitamin D with its anti-inflammatory and immunomodulatory actions may have relieving effects on ocular discomfort and vision-related complaints related with dry eye. To test this hypothesis we statistically examined the correlation of OSDI, TBUT, the Schirmer's test I scores and ocular surface fluorescein staining results of postmenopausal women with severe, moderate vitamin D deficiency and optimal vitamin D levels.

Materials and Methods

This prospective cross-sectional study was approved by the ethics board of the University of Health Sciences, Etilik Zübeyde Hanım Women's Health Education and Research Hospital and the guidelines followed were in accordance with the tenets of the Declaration of Helsinki. Written informed consents were obtained from all patients according to the ethics board guidelines. The subjects consisted of postmenopausal women referred from Internal Medicine and Gynecology outpatient clinics

to the Ophthalmology outpatient clinic because of complaints of ocular discomfort between March 2018 and July 2018. Patients with Sjögren's Syndrome, chronic inflammatory and autoimmune diseases; ocular infectious, allergic and cicatricial diseases; eyelid abnormalities; contact lens users, systemic β blocker, antihistaminic estrogen, and any ophthalmic eye drop users and patients underwent any ocular surgeries within last 6 months were excluded from the study. A total of 87 postmenopausal women participated and all patients had serum vitamin D level measurements before referral to the ophthalmology outpatient clinic. After thorough clinical history was taken, comprehensive ophthalmologic examination including dry eye investigations, TBUT, Schirmer's test I and ocular surface fluorescein staining were performed. OSDI questionnaire was applied to detect patient discomfort and vision-related complaints. Patients were divided into three groups: the first group included patients with severe vitamin D deficiency (n= 30), second group included patients with moderate deficiency (n=27) and the third group included patients with optimal vitamin D levels (n=30).

Vitamin D measurement

Because of the longer plasma half-life (2 weeks) and higher circulating concentrations, 25(OH)D is the most stable form of vitamin D and serum 25(OH)D measurement is indicative of the body vitamin D storage and status. Peripheral blood samples were collected from each patient after 8 hours of fasting and transported to a certified laboratory. Serum 25(OH)D levels were measured by liquid chromatography/mass spectrometry technique (ThermoFisher Scientific). Optimal level of serum 25(OH)D is >26,8 ng/ml; moderate deficiency is defined as serum vitamin D levels 10,24-26,8 ng/ml and severe deficiency is defined as serum 25(OH)D <10,24ng/ml.

DES evaluation

Dry eye evaluation was made by OSDI questionnaire, TBUT, the Schirmer test, ocular surface fluorescein staining. TBUT is a measure of tear film stability and quality. For TBUT evaluation fluorescein strips (ERC Fluorescein Sodium Strip, Turkey) were placed in the lower conjunctival fornices and patient was asked to blink for a few seconds. After the strips were removed, the patient was asked to blink and then open eyes steady. The time in seconds until the first defect in tear film developed was recorded and the mean of three consecutive measurements was accepted as TBUT. The Schirmer's test I evaluates tear volume and the integrity of the lacrimal secretion system. Patients were instructed to look up and test strips (ERC Schirmer Tear Test Strip, Turkey) were hooked over the lateral two-thirds of the lower lid and kept there for 5 minutes. The amount of wetting is measured in millimeters. Ocular surface fluorescein staining was evaluated after fluorescein sodium was applied on the ocular surface and after a few blinks were recorded as present or absent in respect to corneal and conjunctival staining. DES was diagnosed according to the expert's consensus on the clinical diagnosis and treatment of dry eye (2013). The diagnostic criteria: (1) subjective symptoms of dryness and TBUT test \leq 5 seconds or the Schirmer's test without surface anesthesia \leq 5 mm/5 minutes; (2) subjective symptoms of dryness and TBUT test 5-10 seconds or the Schirmer's test without anesthesia 5-10 mm/ 5 seconds combined with positive corneal fluorescein staining.

OSDI Questionnaire

OSDI (Allergan, Irvine CA) is a DES specific questionnaire developed by the Outcomes Research Group at Allergan. It consists of 4 questions on vision-related functions, 5 questions regarding eye symptoms and 3 questions about environmental triggers on DES. Each question is scored from 0 to 4 and the total OSDI score is calculated according to a standard formula. OSDI score < 13 is defined as normal; scores 13 and above are defined as DES. The validity of OSDI on DES symptoms and vision-related quality of life is confirmed by studies.

Statistics

All statistical analyses were performed with IBM SPSS Statistics version 24. One-Sample Kolmogorov-Smirnov test was used to check the normality of data distribution in each group. Patient characteristics were described using means and standard deviations for continuous variables and percentages and standard errors for categorical variables. The Kruskal-Wallis test was used to analyze the association between groups for continuous variables. The Chi-Square test was used to analyze the association between groups for categorical variables p -value < 0.05 indicated statistical significance.

Results

The clinical characteristics of the study groups are given in Table 1. The mean age of Group 1 was 56 ± 10 (range 38-78), Group 2 was 54 ± 6 (range 44-70), and Group 3 was 56 ± 8 (range 72-74) years ($p = 0.60$).

Although the numbers and percentages of dry eye patients, diagnosed according to the experts' consensus on dry eye criteria (2013) decreased as serum vitamin D levels increased, the correlation was not statistically significant ($p = 0.29$).

The mean OSDI scores, the Schirmer's test I levels, and TBUT levels of the groups are given in Table 2. There was no statistically significant difference between groups with respect to mean OSDI scores ($p = 0.80$), the Schirmer's test I values ($p = 0.72$), and TBUT values ($p = 0.33$). Additionally, there was no any statistically significant difference between groups in terms of corneal fluorescein staining results. ($p = 0.25$)

Discussion

Vitamin D, both a prohormone and vitamin, has receptors in virtually all cell types and has actions in cell proliferation and differentiation, regulation of innate and adaptive immunity [2]. In the eye, vitamin D receptors (VDR) are present on the corneal, lens, and ciliary body epithelial cells, retinal pigment epithelium, corneal endothelial cells, ganglion cells, and photoreceptors. The two potential pathways of vitamin D to enter the eye are either via the circulation or through UV-B induced synthesis. Lin et al. [11] have detected measurable concentrations of vitamin D in tear fluid and in aqueous and vitreous humor; they have shown that tear and aqueous humor 25(OH) D and 24,25 (OH) D₂ levels have increased after dietary vitamin D supplementation. In addition, the corneal limbal epithelial cells are able to produce vitamin D, de novo, in culture when exposed to UVB radiation, similar to the cells of the skin [12].

In vivo study by Dang et al. [13], they have shown that vitamin D inhibits proinflammatory cytokines IL-1 α and TNF α on corneal grafts and it has significantly suppressed graft rejection and inhibited corneal neovascularization in rat keratoplasty models. In addition, studies have shown that decreased ionized calcium levels in VDR deficient animals, caused the rate of corneal epi-

Table 1. Clinical characteristics of the study groups

		Group 1 (n=30)	Group 2 (n=27)	Group 3 (n=30)	p value
Age (years)	Mean \pm SD	56 \pm 10	54 \pm 6	56 \pm 8	0.60*
	(Range)	(38-78)	(44-70)	(42-74)	
Vitamin D (ng/ ml)	Mean \pm SD	7.82 \pm 1.80	15.88 \pm 1.70	33.47 \pm 7.0	<0.001*
	(Range)	(4.6-9.9)	(10-21.9)	(27-54)	
Dry Eye	Present n (%)	16 (53.33)	12 (44.44)	10 (33.33)	0.29**
	Absent n	14	15	20	

*: Kruskal-Wallis test; **: Chi-Square test

Table 2. Dry eye parameters of the study groups

		Group 1	Group 2	Group 3	p value
OSDI Score	Mean \pm SD	42.31 \pm 23.51	44.93 \pm 17.47	42.39 \pm 20.38	0.80*
	(Range)	(2.50- 100.00)	(10.00- 69.44)	(7.50- 80.00)	
	Schirmer's test I	Mean \pm SD	9 \pm 5	8 \pm 4	
(Range)	(1-20)	(1-16)	(2-20)		
TBUT	Mean \pm SD	7 \pm 3	7 \pm 3	8 \pm 3	0.33*
	(Range)	(3-17)	(3-15)	(2-12)	
Corneal Staining	Absent (n, %)	22 (73.3%)	22 (81.5%)	27 (90.0%)	0.25**
	Present (n, %)	8 (26.7%)	5 (18.5%)	3 (10.0%)	

OSDI: Ocular Surface Disease Index; TBUT: Tear breakup time; *:Kruskal-Wallis test; **:Chi-Square test

thelial wound healing to decrease and mucin packaging in conjunctival goblet cells to be altered [14,15]. Vitamin D may play a role in Sjögren Syndrome (SS) pathogenesis and low levels of vitamin D have been found in SS patients [16]. These studies suggest that vitamin D with anti-inflammatory actions and positive effects on corneal epithelial cells and goblet cells may have relieving effects on dry eye symptoms and signs. Massingale et al. [17] have found a correlation between tear IL-6 levels and dry eye complaints of burning, discomfort, and pain. Shetty et al. [18] have found that decreased vitamin D levels were associated with exaggerated symptoms. In our study, we did not find any difference between mean OSDI scores of the groups. The mean OSDI scores and percentages of dry eye patients were high and these results may be explained by the elder age group and postmenopausal hormonal status of the patients. Supporting this, studies have shown that dry eye prevalence increases with advancing age and female gender [19,20].

In our study, although the percentages of dry eye patients increased as the serum vitamin D levels decreased, this was not statistically significant. There are conflicting results about the relationship between dry eye disease and serum vitamin D levels in literature. Jee et al. [21] had not found an association between serum vitamin D levels and dry eye syndrome in a study conducted on 16 396 participants over 19 years of age. Jeon et al. [22] in a study conducted on 740 participants in the Study Group for Environmental Eye Disease, had found no association between serum vitamin D levels and dry eye disease. Additionally, Kim et al. [23] had found no association between severe vitamin D deficiency and dry eye syndrome in the adjusted model.

On the other hand, Meng et al. [24] have found a significant association between serum 25(OH)D levels and DES incidence in a study conducted on 70 DES patients and 70 controls.

We did not find any statistically significant difference between the mean Schirmer's test I and TBUT scores of the three groups respectively. Kurtul et al. [25] demonstrated that vitamin D deficiency decreased TBUT and Schirmer's test values in non-Sjögren Syndrome dry eye patients. Similar to our study, Shetty et al. [18] have not found any significant correlation between vitamin D levels and DES parameters. Meng et al. [24] have found a positive correlation between serum 25(OH)D levels and Schirmer's test I scores and conflicting to this, they have found a negative correlation between serum 25(OH)D levels and TBUT scores.

A major strength of our study is that this is the first study to assess and compare dry eye parameters in three groups with moderate and severe vitamin D deficiency and optimal vitamin D levels in postmenopausal women. Our study has several limitations to interpret the results. First, we measured tear parameters at a single time point but DES is a disease with temporal variations. Secondly, the sample size was relatively small because of being a hospital-based study and larger sample sizes and population-based studies are required to confirm results. Thirdly, our study group consisted of postmenopausal women and we expect a high incidence of dry eye because of the elder age and hormonal status.

In conclusion, the present study revealed no significant association between serum vitamin D levels and dry eye parameters in postmenopausal women. Further studies are required to confirm the results.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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